

BICYCLIC AROMATIC COMPOUNDS

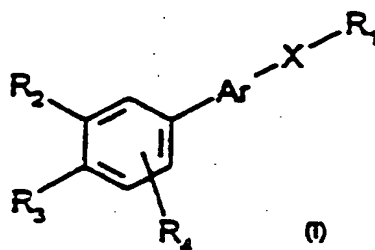
109 *Brief Summary of the Invention*
The invention relates to bicyclic aromatic

compounds as novel and useful industrial products. It also relates to the use of these novel compounds in
5 pharmaceutical compositions intended for use in human or veterinary medicine, or alternatively in cosmetic compositions.

The compounds according to the invention have pronounced activity in the fields of cell differentia-
10 tion and cell proliferation, and find applications more particularly in the topical and systemic treatment of dermatological complaints associated with a disorder of keratinization, dermatological (or other) complaints with an inflammatory and/or immunoallergic component,
15 and dermal or epidermal proliferations, these being either benign or malignant. These compounds may also be used in the treatment of degenerative diseases of connective tissue, for combating both light-induced and chronological ageing of the skin and for treating
20 disorders of cicatrization. They moreover find an application in the ophthalmological field, in particular in the treatment of corneopathies.

The compounds according to the invention may also be used in cosmetic compositions for body and hair
25 hygiene.

109B1 *Brief Description of the Figures*
The compounds according to the invention may be represented by the general formula (I) below:



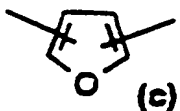
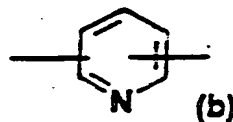
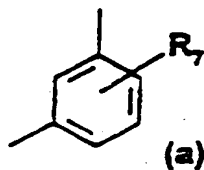
in which:

- R_1 represents (i) the $-CH_3$ radical
- (ii) the radical $-CH_2OR_5$,
- (iii) the radical $-COR_6$

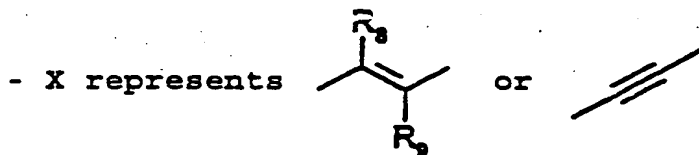
5

R_5 and R_6 having the meaning given below

- Ar represents a radical chosen from the radicals of formulae (a) - (e) below:



R_5 and R_7 having the meaning given below,



R_8 and R_9 having the meanings given below

- R_8 and R_9 , which may be identical or different,

10

represent

(i) a hydrogen atom,

(ii) an alkyl radical having at least
3 carbon atoms, among which the carbon attached to the
phenyl radical is substituted with at least two carbon
atoms,

(iii) a radical $-OR_5$,

(iv) a radical $-SR_5$,

R_5 having the meaning given below,

it being understood that R_2 and R_3 , taken together,
may form with the adjacent aromatic ring a 5- or
6-membered ring optionally substituted with methyl
groups and/or optionally interrupted by an oxygen or
sulphur atom,

and it being understood that R_2 and R_3 cannot at
the same time have the meanings (i), (iii) and (iv)
mentioned above,

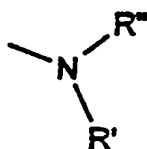
- R_4 and R_7 , which may be identical or different,
represent a hydrogen atom, a halogen atom, a linear or
branched alkyl radical having from 1 to 20 carbon atoms
or a radical $-OR_5$,

- R_5 represents a hydrogen atom, a lower alkyl
radical or a radical $-COR_{10}$

R_{10} having the meaning given below,

- R_6 represents:

- (a) a hydrogen atom
(b) a lower alkyl radical
(c) a radical of formula:



R' and R'' having the meaning given below,

(d) a radical -OR₁₁

R₁₁ having the meaning given below,

- R₈ and R₉, which may be identical or different,
5 represent a hydrogen atom or a lower alkyl radical,
- R₁₀ represents a lower alkyl radical,
- R₁₁ represents a hydrogen atom, a linear or
branched alkyl radical having from 1 to 20 carbon
atoms, an alkenyl radical, a mono- or polyhydroxyalkyl
10 radical, an optionally substituted aryl or aralkyl
radical, a sugar residue or an amino acid or peptide
residue,
- R' and R'', which may be identical or different,
represent a hydrogen atom, a lower alkyl radical, a
15 mono- or polyhydroxyalkyl radical, an optionally
substituted aryl radical or an amino acid or sugar
residue, or alternatively, taken together form a
heterocycle.

The invention is also directed towards the
20 salts of the compounds of formula (I) when R₁ represents
a carboxylic acid function and the geometrical and
optical isomers of the said compounds of formula (I).

When the compounds according to the invention
are in the form of salts, they are preferably salts of

an alkali metal or alkaline-earth metal, or alternatively of zinc or of an organic amine.

According to the present invention, the term lower alkyl radical is understood to refer to a radical having from 1 to 12, preferably from 1 to 9, carbon atoms, advantageously the methyl, ethyl, propyl, isopropyl, butyl, tert-butyl, pentyl, hexyl, heptyl, nonyl, decyl and dodecyl radicals.

The expression linear alkyl radical having from 1 to 20 carbon atoms is understood to refer in particular to the methyl, ethyl, propyl, pentyl, hexyl, octyl, decyl, dodecyl, hexadecyl and octadecyl radicals.

The expression branched alkyl radical having from 1 to 20 carbon atoms is understood to refer in particular to the 2-ethylhexyl, 2-methylbutyl, 2-methylpentyl, 1-methylhexyl and 3-methylheptyl radicals.

Among the alkyl radicals having at least 3 carbon atoms, where the carbon attached to the phenyl radical is substituted with at least two carbon atoms, mention may be made of the tert-butyl, isopropyl, 1,1-dimethylhexyl and 1,1-dimethyldecyl radical. Preferably, these radicals have not more than 20 carbon atoms, even more preferably not more than 12 carbon atoms. Advantageously, the radical (ii) is the tert-butyl radical.

Among the monohydroxyalkyl radicals, a

09619584-071900

radical having 2 or 3 carbon atoms, in particular a 2-hydroxyethyl, 2-hydroxypropyl or 3-hydroxypropyl radical, is preferred.

Among the polyhydroxyalkyl radicals, a radical having from 3 to 6 carbon atoms and from 2 to 5 hydroxyl groups, such as the 2,3-dihydroxypropyl, 2,3,4-trihydroxybutyl or 2,3,4,5-tetrahydroxypentyl radicals or the pentaerythritol residue, is preferred.

Among the aryl radicals, a phenyl radical optionally substituted with at least one halogen atom, a hydroxyl or a nitro function is preferred.

Among the aralkyl radicals, the benzyl or phenethyl radical optionally substituted with at least one halogen atom, a hydroxyl or a nitro function is preferred.

Among the alkenyl radicals, a radical containing from 2 to 5 carbon atoms and having one or more ethylenic unsaturations, more particularly such as the allyl radical, is preferred.

The term sugar residue is understood to refer to a residue derived in particular from glucose, galactose or mannose, or alternatively from glucuronic acid.

The term amino acid residue is understood to refer in particular to a residue derived from lysine, from glycine or from aspartic acid, and the term peptide residue is understood to refer more particularly to a dipeptide or tripeptide residue.

00619584-01900

resulting from the combination of amino acids.

Lastly, the term heterocycle is understood to refer preferably to a piperidino, morpholino, pyrrolidino or piperazino radical optionally substituted in position 4 with a C₁-C₆ alkyl or a mono- or polyhydroxyalkyl radical as defined above.

When the radicals R₁ and R₂ represent a halogen atom, this is preferably a fluorine, bromine or chlorine atom.

Among the compounds of formula (I) above which fall within the scope of the present invention, mention may be made in particular of the following:

- 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-acrylic acid,
- 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-propionic acid,
- 2-(3-tert-Butyl-4-methoxyphenyl)-4-thiophene-acrylic acid,
- 4-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-acrylic acid,
- 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid,
- 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid,
- 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiopheneacrylic acid,
- 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenepropionic acid,

00619584-071900

- 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylpropionic acid,

- N-Methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrroleacrylic acid,

5 - 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,

- N-Methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid,

10 - 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid,

- 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

- 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylpropionic acid,

15 - 2-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

- 2-Propyloxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

20 - 2-Heptyloxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

- 2-Methoxymethoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

- 2-Hydroxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

25 - 3-(3-Methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,

- 3-(3-Propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,

006720" 4856T960

- 3-(3-Heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,
- 3-(3-Methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,
- 5 - 3-(3-Hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,
- 3-(4,4,7-Trimethylthiochroman-6-yl)-phenylacrylic acid,
- N-Ethyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylamide,
- 10 - N-(4-Hydroxyphenyl)-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylamide,
- 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid morpholide,
- 15 - Ethyl 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate,
- 3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoic acid,
- 4-Methoxymethoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,
- 20 - 4-Hydroxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,
- 4-Methoxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,
- 25 - 4-Propyloxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,
- 4-Heptyloxy-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

006720-48567960

- 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]acrolein,

- 3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]prop-2-en-1-ol,

5 - cis-3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoic acid,

- cis-3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid,

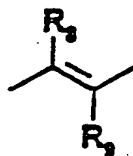
10 - 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-3-pyridineacrylic acid,

- 3-(3-Butyl-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid,

- 6-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyridineacrylic acid.

15 According to the present invention, the compounds of formula (I) more particularly preferred are those for which at least one, and preferably all, of the following conditions are satisfied:

- 20 - R_1 represents the radical $-COR_2$
 - Ar represents the radicals of formula (a) or (d)
 - X represents the radical



- R_2 and R_3 , taken together, form, with the adjacent aromatic ring, a 5- or 6-membered ring optionally substituted with methyl groups and/or

optionally interrupted by an oxygen or sulphur atom.

The subject of the present invention is also processes for the preparation of the compounds of formula (I), in particular according to the reaction
5 scheme given in Figure 1.

Thus, the derivatives of formula (Ia) may be obtained (Fig. 1) from aldehyde or ketone derivatives (5) according to a Horner-type reaction with a lithium or sodium derivative of a phosphonate (7). The carbonyl
10 compounds (5) may be obtained:

- either by a coupling reaction between a boronic acid (3) and a halo derivative (4). This reaction is carried out in the presence of a palladium catalyst, for example tetrakis(triphenylphosphine)-
15 palladium according to the conditions described by N. Miyaura et al., Synthetic Communications (1981) 11(7), 513-519. The boronic acid derivative (3) may be obtained, for example, from the halo derivative (1) by conversion into the lithium reagent (2), followed by
20 reaction with trimethyl borate and hydrolysis.

- or by a coupling reaction between a zinc derivative (8) and a halogenated ester derivative (9) in the presence of a catalyst, for example a palladium or a nickel derivative (NiCl₂, dppe), followed by
25 conversion of the ester function (10) into alcohol (11) and oxidation to aldehyde (5).

The compounds of formula (Ib) may be obtained (Fig. 1) from the acetylenic derivative (6) by reaction

006T40"4856T960

with n-butyllithium and then carboxylation in the presence of CO_2 . The acetylenic compounds (6) may be obtained either:

5 - from aldehyde derivatives (5) (when R_1 is a hydrogen atom), by reaction with carbon tetrabromide and triphenylphosphine in order to give a 2',2'-dibromostyrene derivative which is converted into acetylenic derivative by a non-nucleophilic base such as n-butyllithium, in an aprotic solvent such as
10 tetrahydrofuran.

 - from ketone derivatives (5) (when R_1 is a lower alkyl) by a reaction sequence comprising treatment with a base such as lithium diisopropylamide and then with a dialkyl phosphate chloride and again
15 with lithium diisopropylamide.

 When R_1 represents the radical $-\text{COOH}$, the compounds are prepared by protecting R_1 with a protecting group of alkyl, allylic, benzylic or tert-butyl type.

20 The passage to the free form may be carried out:

 - in the case of an alkyl protecting group, using sodium hydroxide or lithium hydroxide in an alcoholic solvent such as methanol, or in THF.

25 - in the case of an allylic protecting group, using a catalyst such as certain transition metal complexes in the presence of a secondary amine such as morpholine.

00619584-071900

- in the case of a benzylic protecting group, by debenzylation in the presence of hydrogen using a catalyst such as palladium-on-charcoal.

- in the case of a protecting group of tert-butyl type, using trimethylsilyl iodide.

The subject of the present invention is also, as medicinal product, the compounds of formula (I) as defined above.

Some of these compounds are active in a test which consists in identifying molecules that are RXR agonists, as described in French patent application No. 95/07301 filed on 19 June 1995 by the Applicant. This test comprises the following steps: (i) a sufficient amount of a compound which is an active ligand of at least one receptor of the steroidal/thyroidal receptor superfamily, other than a ligand which is specific for the RXR receptors, and which can heterodimerize with RXRs, such as an RAR-agonist molecule, is applied topically to part of the skin of a mammal, (ii) a molecule capable of exhibiting RXR-agonist activity is administered systemically or topically to this same part of the mammal's skin, before, during or after step (i), and (iii) the response on that part of the mammal's skin thus treated is evaluated. Thus, the response to a topical application, to a mammal's ear, of an RAR-agonist molecule, which corresponds to an increase in the thickness of this ear, may be increased by the systemic

00619584 01900

or topical administration of an RXR-agonist molecule. Some of the compounds according to the invention are also active in the test of differentiation of mouse embryonic teratocarcinoma cells (F9) (Cancer Research 43, pp. 5268, 1983) and/or in the test of inhibition of ornithine decarboxylase after induction with TPA in mice (Cancer Research 38, pp. 793-801, 1978). These tests show the activities of these compounds in the fields of cell differentiation and cell proliferation respectively.

The compounds according to the invention are particularly suitable in the following fields of treatment:

1) For treating dermatological complaints associated with a keratinization disorder which has a bearing on differentiation and on proliferation, in particular for treating common acne, comedones, polymorphonuclear leukocytes, rosacea, nodulocystic acne, acne conglobata, senile acne and secondary acnes such as solar, medication-related or profession-related acne.

2) For treating other types of keratinization disorder, in particular ichthyosis, ichthyosiform states, Darier's disease, palmoplantar keratoderma, leucoplasias and leucoplasiform states, and cutaneous or mucous (buccal) lichen.

3) For treating other dermatological complaints associated with a keratinization disorder with an inflammatory and/or immunoallergic component and, in

00619584-071900

particular, all forms of psoriasis, whether it is cutaneous, mucous or unguis psoriasis and even psoriatic rheumatism, or alternatively cutaneous atopy, such as eczema or respiratory atopy or alternatively gingival hypertrophy; the compounds may also be used for some inflammatory complaints which show no keratinization disorder,

- 4) For treating all dermal or epidermal hyperproliferations, whether benign or malignant and whether they are of viral origin or otherwise, such as common warts, flat warts and verruciform epidermodysplasia, it being possible for the oral or florid papillomatoses and the hyperproliferations to be induced by ultraviolet radiation, in particular in the case of basocellular and spinocellular epithelioma,
- 5) For treating other dermatological disorders such as bullosis and collagen diseases,
- 6) For treating certain ophthalmological disorders, in particular corneopathies,
- 7) For repairing or combating ageing of the skin, whether this is light-induced or chronological ageing, or for reducing actinic keratoses and pigmentations, or any pathologies associated with chronological or actinic ageing,
- 8) For preventing or curing the stigmata of epidermal and/or dermal atrophy induced by local or systemic corticosteroids, or any other form of cutaneous atrophy,

00619584-071900

- 9) For preventing or treating cicatrization disorders or for preventing or repairing vibices,
- 10) For combating disorders of sebaceous functioning such as the hyperseborrhoea of acne or simple
- 5 seborrhoea,
- 11) In the treatment or prevention of cancerous or precancerous states,
- 12) In the treatment of inflammatory complaints such as arthritis,
- 10 13) In the treatment of any general or skin complaint of viral origin,
- 14) In the prevention or treatment of alopecia,
- 15) In the treatment of dermatological or general complaints having an immunological component,
- 15 16) In the treatment of complaints of the cardiovascular system such as arteriosclerosis or hypertension, as well as insulin-independent diabetes,
- 17) In the treatment of skin disorders caused by exposure to UV radiation.

20 In the therapeutic fields mentioned above, the compounds according to the invention may advantageously be employed in combination with other compounds having retinoid-type activity, with D vitamins or derivatives thereof, with corticosteroids,

25 with anti-free-radical agents, α -hydroxy or α -keto acids or derivatives thereof, or alternatively with ion-channel blockers. The expression D vitamins or derivatives thereof is understood to refer, for

006T20-1856T950

example, to vitamin D₂ or D₃ derivatives and in particular 1,25-dihydroxy vitamin D₃. The expression anti-free-radical agent is understood to refer, for example, to α -tocopherol, superoxide dismutase, ubiquinol or certain metal-chelating agents. The expression α -hydroxy or α -keto acids or derivatives thereof is understood to refer, for example, to lactic acid, malic acid, citric acid, glycolic acid, mandelic acid, tartaric acid, glyceric acid or ascorbic acid or salts, amides or esters thereof. Lastly, the expression ion-channel blockers is understood to refer, for example, to Minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and derivatives thereof.

The subject of the present invention is also medicinal compositions containing at least one compound of formula (I) as defined above, one of the optical or geometric isomers thereof or one of the salts thereof.

The subject of the present invention is thus a novel medicinal composition intended in particular for treating the abovementioned complaints, and which is characterized in that it comprises, in a pharmaceutically acceptable support which is compatible with the mode of administration selected for this composition, at least one compound of formula (I), one of the optical or geometric isomers thereof or one of the salts thereof.

The compounds according to the invention may be administered enterally, parenterally, topically or

09619584-071900

ocularly.

Via the enteral route, the medicinal products may be in the form of tablets, gelatin capsules, sugar-coated tablets, syrups, suspensions, solutions, powders, granules, emulsions, microspheres or nanospheres or polymeric or lipid vesicles which allow controlled release. Via the parenteral route, the compositions may be in the form of solutions or suspensions for infusion or for injection.

The compounds according to the invention are generally administered at a daily dose of about 0.01 mg/kg to 100 mg/kg of body weight, taken in 1 to 3 doses.

Via the topical route, the pharmaceutical compositions based on compounds according to the invention are more particularly intended for treating the skin and mucous membranes and may, in this case, be in the form of ointments, creams, milks, salves, powders, impregnated pads, solutions, gels, sprays, lotions or suspensions. They may also be in the form of microspheres or nanospheres or polymeric or lipid vesicles or polymeric patches and hydrogels which allow controlled release. These topical-route compositions may moreover be either in anhydrous form or in an aqueous form, depending on the clinical indication.

Via the ocular route, they are mainly eyedrops.

The compositions for topical or ocular use

00619584-01900

contain at least one compound of formula (I) defined above, or one of the optical or geometric isomers thereof, or alternatively one of the salts thereof, at a concentration preferably of between 0.001% and 5% by weight relative to the total weight of the composition.

The compounds of formula (I) according to the invention also find an application in the cosmetic field, in particular in body and hair hygiene and especially for treating skin-types with a tendency towards acne, for promoting the regrowth of the hair, for combating hair loss, for controlling the greasy appearance of the skin or the hair, in protection against the harmful effects of sunlight or in the treatment of physiologically dry skin-types, and for preventing and/or combating light-induced or chronological ageing.

In the cosmetic field, the compounds according to the invention may also advantageously be employed in combination with other compounds having retinoid-type activity, with D vitamins or derivatives thereof, with corticosteroids, with anti-free-radical agents, α -hydroxy or α -keto acids or derivatives thereof, or alternatively with ion-channel blockers, all of these different products being as defined above.

The present invention is this also directed towards a cosmetic composition which is characterized in that it comprises, in a cosmetically acceptable support which is suitable for topical application, at

00619584-071900

least one compound of formula (I) as defined above, or one of the optical or geometric isomers thereof or one of the salts thereof, it being possible in particular for this cosmetic composition to be in the form of a cream, a milk, a lotion, a gel, microspheres or nanospheres or polymeric or lipid vesicles, a soap or a shampoo.

The concentration of compound of formula (I) in the cosmetic compositions according to the invention is advantageously between 0.001% and 3% by weight relative to the composition as a whole.

The medicinal and cosmetic compositions according to the invention may also contain inert additives or even pharmacodynamically or cosmetically active additives or combinations of these additives and, in particular, wetting agents; depigmenting agents such as hydroquinone, azelaic acid, caffeic acid or kojic acid; emollients; moisturizing agents such as glycerol, PEG 400, thiamorpholinone and derivatives thereof, or urea; anti-seborrhoea or anti-acne agents such as S-carboxymethylcysteine, S-benzylcysteamine, the salts and the derivatives thereof, or benzoyl peroxide; antibiotics such as erythromycin and esters thereof, neomycin, clindamycin and esters thereof, and tetracyclines; antifungal agents such as ketoconazole or 4,5-polymethylene-3-isothiazolidones; agents for promoting the regrowth of the hair, such as minoxidil (2,4-diamino-6-piperidinopyrimidine 3-oxide) and

00619584-071900

derivatives thereof, diazoxide (7-chloro-3-methyl-1,2,4-benzothiadiazine 1,1-dioxide) and phenytoin (5,4-diphenylimidazolidine-2,4-dione); non-steroidal anti-inflammatory agents; carotenoids and, in particular, b-carotene; anti-psoriatic agents such as anthraline and derivatives thereof and, lastly, eicosa-5,8,11,14-tetraynoic acid and eicosa-5,8,11-triynoic acid, the esters and the amides thereof.

The compositions according to the invention may also contain flavour-enhancing agents, preserving agents such as para-hydroxybenzoic acid esters, stabilizing agents, moisture regulators, pH regulators, osmotic pressure modifiers, emulsifying agents, UV-A and UV-B screening agents, and antioxidants such as α -tocopherol, butylhydroxyanisole or butylhydroxytoluene.

Several examples of the production of active compounds of formula (I) according to the invention, as well as various solid formulations based on such compounds, will now be given by way of illustration and with no limitation. In the preceding description and the following examples, percentages are given by weight unless otherwise stated.

EXAMPLE 1

5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-acrylic acid

(a) Methyl 5-(3-tert-butyl-4-methoxyphenyl)-2-thiophenecarboxylate

00619584-071900

006T20-1856T960

A solution of 2 g (8.2 mmol) of 3-tert-butyl-4-methoxybromobenzene is added dropwise to a suspension of 300 mg (12 mmol) of magnesium in 10 ml of THF. Once the addition is complete, the mixture is refluxed for one hour. At room temperature, 1.35 g (9.9 mmol) of anhydrous zinc chloride are added and the mixture is stirred for one hour. 1.2 g (5.5 mmol) of methyl 5-bromo-2-thiophenecarboxylate and 60 mg (0.12 mmol) of the $\text{NiCl}_2/\text{DPPE}$ complex are then added successively and the mixture is left stirring at room temperature for 12 hours. The reaction medium is poured into ice-water and extracted with ethyl ether and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is chromatographed on a column of silica eluted with a mixture of hexane and dichloromethane (50/50% by volume). After evaporation of the solvents, 1.56 g (93%) of the expected methyl ester are collected, with a melting point of 94-5°C.

(b) 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophenemethanol

1.5 g (5 mmol) of the above methyl ester and 50 ml of anhydrous THF are introduced into a three-necked flask under a stream of nitrogen. 280 mg (7.4 mmol) of lithium aluminium hydride are added and the mixture is refluxed for four hours. It is hydrolyzed with potassium sodium tartrate solution, the salt is filtered off and the filtrate is evaporated.

The residue obtained is purified by chromatography on a column of silica eluted with a mixture of dichloromethane and hexane (70/30% by volume). After evaporation of the solvents, 1.26 g (92%) of the expected alcohol are recovered, in the form of a colourless oil.

(c) 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-carboxaldehyde

7.15 g (19 mmol) of pyridinium dichromate and 350 ml of dichloromethane are introduced into a round-bottomed flask. A solution of 3.9 g (14 mmol) of 5-(3-tert-butyl-4-methoxyphenyl)-2-thiophenemethanol in 50 ml of dichloromethane is added dropwise, at 0°C, and the mixture is stirred at room temperature for two hours. The reaction medium is filtered through silica and, after evaporation, 3.26 g (84%) of the expected aldehyde are recovered, in the form of a brown oil.

(d) Ethyl 5-(3-tert-butyl-4-methoxyphenyl)-2-thiopheneacrylate

200 mg (6.6 mmol) of sodium hydride (80% in oil) and 50 ml of dimethoxyethane are introduced into a three-necked flask under a stream of nitrogen and a solution of 1.3 ml (6.6 mmol) of triethyl phosphoacetate in 10 ml of dimethoxyethane is added dropwise. The mixture is stirred at room temperature for one hour and then, at 0°C, a solution of 1.5 g (5.5 mmol) of 5-(3-tert-butyl-4-methoxyphenyl)-2-thiophenecarboxaldehyde in 20 ml of dimethoxyethane

006T20" +856T960

is added dropwise. The reaction medium is stirred at room temperature for four hours and is then poured into water and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a mixture of dichloromethane and hexane (30/70% by volume); 1.88 g (100%) of the expected ethyl ester are collected, in the form of a brown oil.

(e) 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-acrylic acid

1.88 g (5.4 mmol) of the above ethyl ester, 20 ml of methanol and 1.88 g (47 mmol) of sodium hydroxide are introduced into a round-bottomed flask and the mixture is refluxed for four hours. The reaction medium is evaporated to dryness, the residue is taken up in water and acidified to pH 1, and the solid is filtered off and dried. The solid obtained is recrystallized from ethanol, filtered off and dried. 1.09 g (63%) of 5-(3-tert-butyl-4-methoxyphenyl)-2-thiopheneacrylic acid are collected, with a melting point of 218-9°C.

EXAMPLE 2

25 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-propionic acid

(a) 2',2'-Dibromo-5-(3-tert-butyl-4-methoxyphenyl)-2-thiopheneethylene

1.79 g (6.5 mmol) of 5-(3-tert-butyl-4-methoxyphenyl)-2-thiophenecarboxaldehyde prepared in Example 1 (c) and 50 ml of dichloromethane are introduced into a round-bottomed flask. 4.32 g (13 mmol) of carbon tetrabromide, 3.41 g (13 mmol) of triphenylphosphine and 850 mg (13 mmol) of zinc powder are successively added and the mixture is stirred at room temperature for two hours. The reaction medium is evaporated and the residue obtained is purified by chromatography on a column of silica eluted with dichloromethane. 2.5 g (89%) of the expected product are collected.

(b) 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-acetylene

2.48 g (5.7 mmol) of 2',2'-dibromo-5-(3-tert-butyl-4-methoxyphenyl)-2-thiopheneethylene and 40 ml of THF are introduced into a three-necked flask under a stream of nitrogen. 5.1 ml (12.7 mmol) of n-butyllithium solution (2.5 M in hexane) are added dropwise, at -78°C, and the mixture is allowed to return to room temperature over one hour. The reaction medium is poured into water and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with heptane. 1.1 g (71%) of the expected acetylenic derivative are collected, in the form of a yellow oil.

00619584-071900

(c) 5-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-
propionic acid

1.1 g (4 mmol) of the above acetylenic
derivative and 20 ml of THF are introduced into a
5 three-necked flask under a stream of nitrogen. 1.95 ml
(4.9 mmol) of n-butyllithium (2.5 M in hexane) are
added dropwise, at -78°C, and the mixture is stirred
for thirty minutes. A stream of CO₂ is passed through at
-78°C for fifteen minutes and the mixture is allowed to
10 return to room temperature. The reaction medium is
poured into aqueous ammonium chloride solution and
extracted with ethyl ether, and the organic phase is
separated out after settling has taken place, dried
over magnesium sulphate and evaporated. The residue
15 obtained is purified by chromatography on a column of
silica eluted with dichloromethane. After evaporation
of the solvents, 300 mg (23%) of 5-(3-tert-butyl-
4-methoxyphenyl)-2-thiophenepropionic acid are
collected, with a melting point of 124-6°C.

20 EXAMPLE 3

2-(3-tert-Butyl-4-methoxyphenyl)-4-thiophene-
acrylic acid

(a) 3-tert-Butyl-4-methoxyphenylboronic acid

4 g (16.5 mmol) of 3-tert-butyl-4-methoxy-
25 bromobenzene and 50 ml of THF are introduced into a
three-necked flask under a stream of nitrogen. 7.9 ml
(19.8 mmol) of n-butyllithium (2.5 M in hexane) are
added dropwise at -78°C, the mixture is stirred for

00619584-071900

15 minutes at this temperature, 5.6 ml (49.5 mmol) of trimethyl borate are added and the mixture is stirred for 2 hours. 20 ml of hydrochloric acid (1 N) are added at -50°C and the mixture is allowed to return to room temperature. The reaction medium is extracted with ethyl ether and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. 3.79 g (100%) of the expected boronic acid are collected, which is used in its present state for the rest of the synthesis.

(b) Ethyl 2-(3-tert-butyl-4-methoxyphenyl)-4-thiophenecarboxylate

260 mg (0.5 mmol) of tetrakis(triphenylphosphine)palladium(0), 50 ml of toluene and 2.59 g (10.9 mmol) of ethyl 2-bromo-4-thiophenecarboxylate are introduced into a three-necked flask under a stream of nitrogen and the mixture is stirred at room temperature for 20 minutes. 3.7 g (16.5 mmol) of 3-tert-butyl-4-methoxyphenylboronic acid and 11 ml of aqueous sodium carbonate solution (2 N) are then added and the mixture is refluxed for 8 hours. The reaction medium is evaporated to dryness, the residue is taken up in water and ethyl ether and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue is purified by chromatography on a column of silica eluted with a mixture of ethyl acetate and heptane (10/90% by volume). 3.53 g (69%) of ethyl 2-(3-tert-butyl-

00619584-071900

4-methoxyphenyl)-4-thiophenecarboxylate are obtained.

(c) 2-(3-tert-Butyl-4-methoxyphenyl)-4-thiophene-
methanol

In a similar manner to Example 1(b), starting
5 with 3.5 g (11 mmol) of ethyl 2-(3-tert-butyl-
4-methoxyphenyl)-4-thiophenecarboxylate, 3.2 g (100%)
of the expected alcohol are obtained in the form of a
brown oil.

(d) 2-(3-tert-Butyl-4-methoxyphenyl)-4-thiophene--
10 carboxaldehyde

In a similar manner to Example 1(c), starting
with 3.2 g (11 mmol) of the above alcohol, 2.3 g (76%)
of 2-(3-tert-butyl-4-methoxyphenyl)-4-thiophene-
carboxaldehyde are obtained in the form of a brown oil.

(e) Ethyl 2-(3-tert-butyl-4-methoxyphenyl)-4-thiophene-
15 acrylate

In a similar manner to Example 1(d), by
reaction of 1.3 g (4.7 mmol) of 2-(3-tert-butyl-
4-methoxyphenyl)-4-thiophenecarboxaldehyde with 1.28 g
20 (5.7 mmol) of triethyl phosphonoacetate, 1.1 g (67%) of
the expected ethyl ester are obtained, with a melting
point of 119-20°C.

(f) 2-(3-tert-Butyl-4-methoxyphenyl)-4-thiophene-
acrylic acid

In a similar manner to Example 1(e), starting
25 with 1.1 g (3.2 mmol) of the above ethyl ester, 750 mg
(74%) of 2-(3-tert-butyl-4-methoxyphenyl)-4-thiophene-
acrylic acid are obtained, with a melting point of

00619584-071900

197-8°C.

EXAMPLE 4

4-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-
acrylic acid

- 5 (a) 4-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-
carboxaldehyde

In a similar manner to Example 3(b), by
reaction of 2.68 g (12.3 mmol) of 3-tert-butyl-
4-methoxyphenylboronic acid with 1.55 g (2.12 mmol) of
10 4-bromo-2-thiophenecarboxaldehyde, 2.13 g (95%) of
4-(3-tert-butyl-4-methoxyphenyl)-2-thiophene-
carboxaldehyde are obtained in the form of a yellow
oil.

- 15 (b) Ethyl 4-(3-tert-butyl-4-methoxyphenyl)-
2-thiopheneacrylate

In a similar manner to Example 1(d), by
reaction of 1.2 g (4.3 mmol) of 4-(3-tert-butyl-
4-methoxyphenyl)-2-thiophenecarboxaldehyde with 1.17 g
(5.2 mmol) of triethyl phosphonoacetate, 1.55 g (100%)
20 of the expected ethyl ester are obtained in the form of
an oil.

- (c) 4-(3-tert-Butyl-4-methoxyphenyl)-2-thiophene-
acrylic acid

In a similar manner to Example 1(e), starting
25 with 1.55 g (4.5 mmol) of the above ethyl ester, 1.14 g
(88%) of 4-(3-tert-butyl-4-methoxyphenyl)-2-thiophene-
acrylic acid are obtained, with a melting point of
206-7°C.

006T20"4856T960

EXAMPLE 55-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid

- 5 (a) 3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid,

In a similar manner to Example 3(a), starting with 5 g (17.8 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-bromonaphthalene, 4.22 g (100%) of boronic acid are obtained.

- 10 (b) 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenecarboxaldehyde

In a similar manner to Example 3(b), by reaction of 4.2 g (17 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 2.17 g (11.3 mmol) of 5-bromo-2-thiophenecarboxaldehyde, 2.1 g (60%) of the expected aldehyde are obtained, with a melting point of 130-5°C.

- 15 (c) Ethyl 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylate

- 20 In a similar manner to Example 1(d), by reaction of 2 g (6.4 mmol) of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenecarboxaldehyde with 1.73 g (7.7 mmol) of triethyl phosphonoacetate, 2.02 g (82%) of the expected ethyl ester are obtained.

- 25 (e) 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid

In a similar manner to Example 1(e), starting

0061954-0-12561960

with 2 g (5.2 mmol) of the above ethyl ester, 1.79 g (96%) of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid are obtained, with a melting point of 175-7°C.

5 EXAMPLE 6

4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid

(a) 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenecarboxaldehyde

10 In a similar manner to Example 3(b), by reaction of 4.2 g (17 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 2.17 g (11.3 mmol) of 4-bromo-2-thiophenecarboxaldehyde, 2.75 g (78%) of the expected aldehyde are obtained, with a melting point of 144-6°C.

(b) Ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylate

20 In a similar manner to Example 1(d), by reaction of 2.7 g (8.6 mmol) of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenecarboxaldehyde with 2.1 ml (10.4 mmol) of triethyl phosphonoacetate, 2.76 g (84%) of the expected ethyl ester are obtained.

25 (c) 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacrylic acid

In a similar manner to Example 1(e), starting with 2.7 g (7.1 mmol) of the above ethyl ester, 2.5 g (98%) of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-

0061584-071900

2-naphthyl)-2-thiopheneacrylic acid are obtained, with a melting point of 215-20°C.

EXAMPLE 7

4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiopheneacrylic acid

- (a) 5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthylboronic acid

In a similar manner to Example 3(a), starting with 5 g (18.7 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-bromonaphthalene, 4.3 g (100%) of the expected boronic acid are obtained.

- (b) 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiophenecarboxaldehyde

In a similar manner to Example 3(b), by reaction of 4.3 g (18.7 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylboronic acid with 2.36 g (12.3 mmol) of 4-bromo-2-thiophenecarboxaldehyde, 2.3 g (63%) of the expected aldehyde derivative are obtained, with a melting point of 84-5°C.

- (c) Ethyl 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiopheneacrylate

In a similar manner to Example 1(d), by reaction of 2.28 g (8.3 mmol) of (5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiophenecarboxaldehyde with 2 ml (9.9 mmol) of triethyl phosphonoacetate, 810 mg (26%) of the expected ethyl ester are obtained, with a melting point of 82-4°C.

- (d) 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-

00619584-071900

2-naphthyl)-2-thiopheneacrylic acid

In a similar manner to Example 1(e), starting with 810 mg (2.2 mmol) of the above ethyl ester, 720 mg (96%) of 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-thiopheneacrylic acid are obtained, with a melting point of 182-5°C.

EXAMPLE 8

5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenepropiolic acid

10 (a) 2',2'-Dibromo-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneethylene

In a similar manner to Example 2(a), starting with 3 g (9.6 mmol) of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophene-15 carboxaldehyde, 4.56 g (100%) of 2',2'-dibromo-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneethylene are obtained.

(b) 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneacetylene

20 In a similar manner to Example 2(b), starting with 4.5 g (9.6 mmol) 2',2'-dibromo-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiopheneethylene, 1.42 g (48%) of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophene-25 acetylene are obtained.

(c) 5-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenepropiolic acid

In a similar manner to Example 2(c), starting

00619584.071900
00619584.071900

with 1.4 g (4.5 mmol) of the above acetylenic derivative, 800 mg (51%) of 5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-thiophenepropiolic acid are obtained, with a melting point of 138-40°C.

5 EXAMPLE 9

3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylpropionic acid

(a) 3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid,

10 100 g (0.356 mol) of 2-bromo-3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthalene and 1 litre of THF are introduced into a two-litre reactor under a stream of nitrogen, and the solution is cooled to -60°C. 157 ml (0.392 mol) of n-butyllithium (2.5 M in hexane) are added dropwise and the mixture is stirred for one hour. 121 ml (1.07 mol) of trimethyl borate are added dropwise at -70°C and the mixture is stirred for one hour. 500 ml of hydrochloric acid (1 N) are added at -35°C and the mixture is allowed to return to room temperature. The reaction medium is extracted with ethyl acetate and the organic phase is separated out after settling has taken place, washed twice with 500 ml of hydrochloric acid (1 N), dried over magnesium sulphate and evaporated. 83 g (95%) of the expected boronic acid are collected.

(b) 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde

700 ml of DME, 2.4 g (2 mmol) of

00619584-071900

tetrakis(triphenylphosphine)palladium(0) and 8.44 g (45.6 mmol) of 3-bromobenzaldehyde are introduced into a three-necked flask under a stream of nitrogen and the mixture is stirred for 10 minutes. A solution of 17 g (69.1 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid in 25 ml of ethanol are then added, followed by 46 ml (91 mmol) of potassium carbonate solution (2 M) and the mixture is refluxed for four hours. The reaction medium is cooled and filtered and the solid is washed with bicarbonate solution and then with ethyl acetate. The solid obtained is recrystallized from ethanol and 7 g (50%) of the expected aldehyde are collected, with a melting point of 104-5°C.

- 15 (c) 2',2'-Dibromo-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylethylene

In a similar manner to Example 2(a), starting with 2 g (6.5 mmol) of the above aldehyde, 1.96 g (65%) of the expected product are obtained in the form of a colourless oil.

- 20 (d) 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacetylene

In a similar manner to Example 2(b), starting with 1.96 g (4.23 mmol) of 2',2'-dibromo-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl-ethylen, 1.29 g (99%) of the expected acetylenic derivative are obtained in the form of a pale yellow oil.

(e) 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylpropionic acid

In a similar manner to Example 2(c), starting with 1.17 g (3.9 mmol) of the above acetylenic derivative, 900 mg (67%) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylpropionic acid are obtained, with a melting point of 180-1°C.

EXAMPLE 10

10 N-Methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrroleacrylic acid

(a) 4-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrrolecarboxaldehyde

In a similar manner to Example 3(b), by reaction of 5.9 g (25.6 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylboronic acid with 3.7 g (21.3 mmol) of 4-bromo-2-pyrrolecarboxaldehyde, 1.3 g (21.6%) of the expected product are obtained, with a melting point of 211-2°C.

20 (b) N-Methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrrolecarboxaldehyde
1.3 g (4.6 mmol) of 4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrrolecarboxaldehyde and 50 ml of THF are introduced into a three-necked flask under a stream of nitrogen. 300 mg (10 mmol) of sodium hydride (80% in oil) are added portionwise and the mixture is stirred until the evolution of gas has ceased. 640 μ l (10 mmol) of iodomethane are then added and the mixture is stirred at room temperature for one

00619584-071900

hour. The reaction medium is poured into water and extracted with ethyl acetate, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue
 5 obtained is purified by chromatography on a column of silica eluted with a mixture of dichloromethane and heptane (70/30). After evaporation of the solvents, 600 mg (44%) of the expected product are collected.

(c) Ethyl N-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-
 10 tetramethyl-2-naphthyl)-2-pyrroleacrylate

In a similar manner to Example 1(d), by reaction of 480 mg (1.3 mmol) of N-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-
 2-pyrrolecarboxaldehyde with 400 μ l (152 mmol) of
 15 triethyl phosphonoacetate, 350 mg of the expected ethyl ester are obtained in the form of an oil.

(d) N-Methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-
 tetramethyl-2-naphthyl)-2-pyrroleacrylic acid

In a similar manner to Example 1(e), starting
 20 with 350 mg (0.94 mmol) of the above ethyl ester, 170 mg (23%) of N-methyl-4-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-2-pyrroleacrylic acid are obtained, with a melting point of 185-6°C.

EXAMPLE 11

25 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid

(a) 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylcarboxaldehyde

00619584-071900

In a similar manner to Example 3(b), by reaction of 6.43 g (27.7 mmol) of 5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthylboronic acid with 2.7 ml (23.1 mmol) of 4-bromobenzaldehyde, 2.05 g (24%) of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)-phenylcarboxaldehyde are obtained in the form of a pale yellow oil.

(b) Ethyl 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylate

In a similar manner to Example 1(d), by reaction of 800 mg (2.7 mmol) of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylcarboxaldehyde with 650 ml (3.3 mmol) of triethyl phosphonoacetate, 900 mg (91%) of the expected ethyl ester are obtained in the form of a colourless oil.

(c) 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid

In a similar manner to Example 1(e), starting with 1.22 g (2.7 mmol) of the above ethyl ester, 380 mg (41%) of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 210-1°C.

EXAMPLE 12

N-Methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid

(a) N-Methyl-4-bromo-2-pyrrolecarboxaldehyde

In a similar manner to Example 10(b), by reaction of 4 g (23 mmol) of 4-bromo-

006T20-4856T960

2-pyrrolicarboxaldehyde with 1.7 ml (27.6 mmol) of iodomethane, 2.3 g (50%) of the expected product are obtained, with a melting point of 123-4°C.

- (b) N-Methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolicarboxaldehyde

In a similar manner to Example 3(b), by reaction of 3 g (12.1 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 1.9 g (10.1 mmol) of N-methyl-4-bromo-2-pyrrolicarboxaldehyde, 1.85 g (59%) of the expected product are obtained in the form of a pale yellow oil.

- (c) Ethyl N-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolicacrylate

In a similar manner to Example 1(d), by reaction of 1.85 g (6 mmol) of N-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolicarboxaldehyde with 1.4 ml (7.2 mmol) of triethyl phosphonoacetate, 2.1 g (92%) of the expected ethyl ester are obtained in the form of an orange-coloured oil.

- (d) N-Methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolicacrylic acid

In a similar manner to Example 1(e), starting with 2 g (5.3 mmol) of the above ethyl ester, 730 mg (39.5%) of N-methyl-4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolicacrylic acid are obtained, with a melting point of 185-6°C.

00619584.01900

EXAMPLE 134-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid

- 5 (a) 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolecarboxaldehyde

In a similar manner to Example 3(b), by reaction of 2.47 g (10 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 1.5 g (8.4 mmol) of 4-bromo-2-pyrrolecarboxaldehyde, 950 mg (38.5%) of the expected aldehyde are obtained, with a melting point of 128-9°C.

- (b) Ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylate

In a similar manner to Example 1(d), by reaction of 500 mg (1.7 mmol) of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrrolecarboxaldehyde with 400 μ l (2 mmol) of triethyl phosphonoacetate, 570 mg (92%) of the expected ethyl ester are obtained.

- 20 (c) 4-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid

In a similar manner to Example 1(e), starting with 570 mg (1.9 mmol) of ethyl 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylate, 240 mg (37%) of 4-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-2-pyrroleacrylic acid are obtained, with a melting point of 245-6°C.

00619584-071900

EXAMPLE 143-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid

In a similar manner to Example 9(b), by
 5 reaction of 73.4 g (0.30 mol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 44.7 g (0.20 mol) of 4-bromophenylacrylic acid, and after recrystallization from ethanol, 48 g (61%) of
 10 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 207-8°C.

EXAMPLE 153-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylpropionic acid

15 (a) 2',2'-Dibromo-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylethylene

In a similar manner to Example 2(a), starting with 2.05 g (7 mmol) of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)benzaldehyde [prepared in
 20 Example 11(a)], 1.07 g (35%) of the expected product are obtained in the form of an oil.

(b) 3-(5,6,7,8-Tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylpropionic acid.

900 mg (2 mmol) of 2',2'-dibromo-3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenyl-
 25 ethylene and 40 ml of THF are introduced into a three-necked flask under a stream of nitrogen. 2.2 ml (5.2 mmol) of n-butyllithium solution (2.5 M in hexane)

00619584-071900

are added dropwise at -50°C and the mixture is allowed to return to room temperature. CO_2 is introduced at 0°C for 20 minutes and the mixture is stirred at room temperature for one hour. The reaction medium is poured into saturated ammonium chloride solution and adjusted to pH 1 with hydrochloric acid, the mixture is extracted with ethyl acetate and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with a mixture of dichloromethane and methanol (95/5). After evaporation of the solvents, 80 mg (12%) of 3-(5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylpropionic acid are collected, with a melting point of $164-5^{\circ}\text{C}$.

EXAMPLE 16

2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid

(a) 2-Hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde.

In a similar manner to Example 9(b), by reaction of 15 g (61 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 8.16 g (41 mmol) of 5-bromo-2-hydroxybenzaldehyde, 11.7 g (89%) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde are obtained, with a melting point of $138-9^{\circ}\text{C}$.

006T20-4856T960

(b) 2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde.

In a similar manner to Example 10(b), by reaction of 2 g (6.2 mmol) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde with 425 μ l (6.8 mmol) of iodomethane, 1.68 g (88%) of the expected product are obtained.

(c) Ethyl 2-methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate.

In a similar manner to Example 1(d), by reaction of 1.65 g (5 mmol) of 2-methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde with 1.68 g (7.5 mmol) of triethyl phosphonoacetate, 1.7 g (83%) of the expected ethyl ester are obtained in the form of an oil.

(d) 2-Methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 1(e), starting with 1.6 g (3.9 mmol) of the above ethyl ester, 1.4 g (93%) of 2-methoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 181-2°C.

EXAMPLE 17

2-Propyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

(a) 2-Propyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde.

In a similar manner to Example 10(b), by

00619584-071900

reaction of 2 g (6.2 mmol) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde [prepared in Example 16(a)] with 670 μ l (6.8 mmol) of 1-iodopropane, 2.2 g (88%) of the expected product are
 5 obtained in the form of a colourless oil.

(b) Ethyl 2-propyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate.

In a similar manner to Example 1(d), by reaction of 2.18 g (6 mmol) of 2-propyloxy-5-
 10 (3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde with 2.03 g (9 mmol) of triethyl phosphonoacetate, 2.13 g (82%) of the expected ethyl ester are obtained in the form form of a yellow oil.

(c) 2-Propyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.
 15

In a similar manner to Example 1(e), starting with 2.1 g (4.8 mmol) of the above ethyl ester, 1.68 g (86%) of 2-propyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained,
 20 with a melting point of 125-6°C.

EXAMPLE 18

2-Heptyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

(a) 2-Heptyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde.
 25

In a similar manner to Exmaple 10(b), by reaction of 2 g (9.3 mmol) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde

[prepared in Example 16(a)] with 1.1 ml (6.8 mmol) of 1-bromoheptane, 1.88 g (72%) of the expected product are obtained in the form of a yellow oil.

(b) Ethyl 2-heptyloxy-5-(3,5,5,8,8-pentamethyl-
5 5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate.

In a similar manner to Example 1(d), by reaction of 1.78 g (4.2 mmol) of 2-heptyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde with 1.44 g (6.3 mmol) of
10 triethyl phosphonoacetate, 1.89 g (90%) of the expected ethyl ester are obtained in the form of a yellow oil.

(c) 2-Heptyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 1(e), starting
15 with 1.89 g (3.9 mmol) of the above ethyl ester, 1.2 g (67%) of 2-heptyloxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 137-8°C.

EXAMPLE 19

20 2-Methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

(a) 2-Methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde.

25 In a similar manner to Example 10(b), by reaction of 3 g (9.3 mmol) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde [prepared in Example 16(a)] with 777 μ l (10.2 mmol) of

methoxymethyl chloride, 3.5 g (100%) of the expected product are obtained in the form of an oil.

(b) Ethyl 2-methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate.

5 In a similar manner to Example 1(d), by reaction of 3.4 g (9.3 mmol) of 2-methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-benzaldehyde with 4.16 g (18.6 mmol) of triethyl phosphonoacetate, 3.5 g (86%) of the expected ethyl ester are obtained, with a melting point of 100-1°C.

10 (c) 2-Methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 1(e), starting with 1.5 g (3.4 mmol) of the above ethyl ester, 1.2 g (86%) of 2-methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 191-2°C.

EXAMPLE 20

20 2-Hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

(a) Methyl 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate

1.9 g (4.35 mmol) of 2-methoxymethoxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid, 20 ml of methanol and 30 ml of THF are introduced into a round-bottomed flask. 2.8 ml of concentrated sulphuric acid are added and the mixture is stirred at room temperature for 12

00619584.071900

hours. The reaction medium is poured into water and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, washed with water, dried over magnesium sulphate and

5 evaporated. 1.63 g (95%) of methyl 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate are collected.

(b) 2-Hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid.

10 In a similar manner to Example 1(e), starting with 1.63 g (4.25 mmol) of the above ethyl ester, 1.3 g (85%) of 2-hydroxy-5-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 204-5°C.

15 EXAMPLE 21

3-(3-Methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

(a) 3-Bromo-2-methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene.

20 7 g (24.7 mmol) of 3-bromo-2-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene and 40 ml of DMF are introduced into a three-necked flask under a stream of nitrogen. 890 mg (29.6 mmol) of sodium hydride (80% in oil) are added portionwise and the
25 mixture is stirred until the evolution of gas has ceased. 1.7 ml (27 mmol) of iodomethane are then added and the mixture is stirred at room temperature for one hour. The reaction medium is poured into water and

00619584-071900

extracted with ethyl ether, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. 7.3 g (99%) of the expected product are collected in the form of an oil which crystallizes slowly. Melting point 77-8°C.

(b) 2-Methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylboronic acid.

In a similar manner to Example 3(a), starting with 6.7 g (22.5 mmol) of 3-bromo-2-methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene, 4.54 g (77%) of the expected boronic acid are obtained, with a melting point of 151-2°C.

(c) 3-(3-Methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 9(b), by reaction of 2.62 g (10 mmol) of 2-methoxy-5,6,7,8-tetramethylnaphthylboronic acid with 1.51 g (6.7 mmol) of 3-bromophenylacrylic acid, 1.1 g (45%) of 3-(3-methoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 187-8°C.

EXAMPLE 22

3-(3-Propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

(a) 3-Bromo-2-propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene.

In a similar manner to Example 21(a), by reaction of 7 g (24.7 mmol) of 3-bromo-2-hydroxy-

5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene with
2.45 ml (27 mmol) of 1-bromopropane, 8.1 g (100%) of
3-bromo-2-propyloxy-5,6,7,8-tetrahydro-5,5,8,8-
tetramethylnaphthalene are obtained in the form of an
5 orange-coloured oil.

(b) 2-Propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetra-
methylnaphthylboronic acid.

In a similar manner to Example 3(a), by
reaction of 8 g (24.6 mmol) of 3-bromo-2-propyloxy-
10 5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene,
5.7 g (80%) of the expected boronic acid are obtained,
with a melting point of 138-9°C.

(c) 3-(3-Propyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetra-
methyl-2-naphthyl)phenylacrylic acid.

15 In a similar manner to Example 9(b), by
reaction of 5 g (17.2 mmol) of 2-propyloxy-5,6,7,8-
tetrahydro-5,5,8,8-tetramethylnaphthylboronic acid with
2.6 g (11.5 mmol) of 3-bromophenylacrylic acid, 1.66 g
(35%) of 3-(3-propyloxy-5,6,7,8-tetrahydro-5,5,8,8-
20 tetramethyl-2-naphthyl)phenylacrylic acid are obtained,
with a melting point of 172-3°C.

EXAMPLE 23

3-(3-Heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-
tetramethyl-2-naphthyl)phenylacrylic acid.

25 (a) 3-Bromo-2-heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-
tetramethylnaphthalene.

In a similar manner to Example 21(a), by
reaction of 7 g (24.7 mmol) of 3-bromo-2-hydroxy-

5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene with
4.24 ml (27 mmol) of 1-bromoheptane, 10 g (100%) of
3-bromo-2-heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-
tetramethylnaphthalene are obtained in the form of a
5 brown oil.

(b) 2-Heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetra-
methylnaphthylboronic acid.

In a similar manner to Example 3(a), starting
with 10 g (26.2 mmol) of 3-bromo-2-heptyloxy-5,6,7,8-
10 tetrahydro-5,5,8,8-tetramethylnaphthalene, 6.1 g (67%)
of the expected boronic acid are obtained, with a
melting point of 102-3°C.

(c) 3-(3-Heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-tetra-
methyl-2-naphthyl)phenylacrylic acid.

15 In a similar manner to Example 9(b), by
reaction of 5 g (14.4 mmol) of 2-heptyloxy-5,6,7,8-
tetrahydro-5,5,8,8-tetramethylnaphthylboronic acid with
2.52 g (11.1 mmol) of 3-bromophenylacrylic acid, 2.7 g
(54%) of 3-(3-heptyloxy-5,6,7,8-tetrahydro-5,5,8,8-
20 tetramethyl-2-naphthyl)phenylacrylic acid are obtained,
with a melting point of 112-3°C.

EXAMPLE 24

3-(3-Methoxymethoxy-5,6,7,8-tetrahydro-
5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic
25 acid.

(a) 3-Bromo-2-methoxymethoxy-5,6,7,8-tetrahydro-
5,5,8,8-tetramethylnaphthalene.

In a similar manner to Example 21(a), by

09619584.071900

reaction of 7 g (24.7 mmol) of 3-bromo-2-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene with 2.05 ml (27 mmol) of methoxymethyl chloride, 8.1 g (100%) of 3-bromo-2-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene are obtained in the form of a light-brown oil.

(b) 2-Methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylboronic acid.

In a similar manner to Example 3(a), starting with 8 g (24.4 mmol) of 3-bromo-2-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthalene, 5.5 g (77%) of the expected boronic acid are obtained, with a melting point of 133-4°C.

(c) 3-(3-Methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 9(b), by reaction of 5.3 g (18.1 mmol) of 2-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethylnaphthylboronic acid with 3.16 g (14 mmol) of 3-bromophenylacrylic acid, 4.39 g (80%) of 3-(3-methoxymethoxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 156-7°C.

EXAMPLE 25

3-(3-Hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

(a) Methyl 3-(3-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylate.

2 g (5 mmol) of 3-(3-methoxymethoxy-5,6,7,8-

005720-48567960

00619584.07.1900

tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid, 10 ml of methanol and 10 ml of THF are introduced into a round-bottomed flask. 2.8 ml of concentrated sulphuric acid are added and the mixture is stirred at room temperature for 6 hours. The reaction medium is poured into water and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, washed with water, dried over magnesium sulphate and evaporated. 1.80 g (98%) of the expected methyl ester are collected, with a melting point of 182-3°C.

(b) 3-(3-Hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid.

In a similar manner to Example 1(e), starting with 1.5 g (4.1 mmol) of the above methyl ester, 1.3 g (90%) of 3-(3-hydroxy-5,6,7,8-tetrahydro-5,5,8,8-tetramethyl-2-naphthyl)phenylacrylic acid are obtained, with a melting point of 244-5°C.

EXAMPLE 26

20 3-(4,4,7-Trimethylthiochroman-6-yl)phenyl-
 acrylic acid.

(a) 1-Methyl-3-(3-methylbut-2-enyl)sulphanylbenzene.

5 g (40 mmol) of 3-methylthiophenol, 5.6 g (40 mmol) of potassium carbonate and 50 ml of DMF are introduced into a three-necked flask. 7.2 g (48 mmol) of 3-methyl-2-butene bromide are added and the mixture is stirred at room temperature for four hours. The

reaction medium is poured into water and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. 7.8 g (100%) of the expected product are collected in the form of a yellow oil.

(b) 4,4,7-Trimethylthiochroman.

7 g (36.4 mmol) of 1-methyl-3-(3-methylbut-2-enyl)sulphanylbenzene and 50 ml of toluene are introduced into a round-bottomed flask and 10.4 g (54.6 mmol) of para-toluenesulphonic acid are added. The mixture is refluxed for four hours. The reaction medium is evaporated to dryness, the residue is taken up in water and ethyl ether and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. 6.8 g (97%) of the thiochroman are collected in the form of a brown oil.

(c) 6-Bromo-4,4,7-trimethylthiochroman.

6.2 g (32.2 mmol) of 4,4,7-trimethylthiochroman, 40 ml of dichloromethane and 90 mg of iron powder are introduced into a three-necked flask. 1.65 ml (32.2 mmol) of bromine are added and the mixture is stirred at room temperature for two hours. The reaction medium is poured into sodium bicarbonate solution and extracted with dichloromethane, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a

00619584-071900

column of silica eluted with heptane. 5.9 g (67%) of the bromo derivative are collected in the form of a pale yellow oil.

(d) 4,4,7-Trimethylthiochromanylboronic acid.

5 In a similar manner to Example 3(a), starting with 5.8 g (21.4 mmol) of 6-bromo-4,4,7-trimethylthiochroman, 3.88 g (76%) of the expected boronic acid are obtained, with a melting point of 252-3°C.

(e) 3-(4,4,7-Trimethylthiochroman-6-yl)phenylacrylic acid.
10 acid.

In a similar manner to Example 9(b), by reaction of 1.5 g (6.3 mmol) of 4,4,7-trimethylthiochromanylboronic acid with 1.2 g (5.3 mmol) of 3-bromophenylacrylic acid, 1.1 g (99%) of 3-(4,4,7-trimethylthiochroman-6-yl)phenylacrylic acid are
15 obtained, with a melting point of 102-3°C.

EXAMPLE 27

N-Ethyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylamide.

20 (a) 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacryloyl chloride.

3.5 g (10 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid and 50 ml of dichloromethane are introduced into a round-bottomed flask and 2 ml (10 mmol) of dicyclohexylamine
25 are added. The mixture is stirred at room temperature for 10 minutes and 729 μ l (10 mmol) of thionyl chloride

are then introduced with stirring for 15 minutes. The reaction medium is evaporated to dryness, the residue is taken up in ethyl ether, the dicyclohexylamine salt is filtered off and the filtrate is evaporated. 3.7 g (100%) of the crude acid chloride are collected, which will be used in its current state for the rest of the synthesis.

(b) N-Ethyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylamide.

20 ml of THF are introduced into a round-bottomed flask and 2.8 ml (35 mmol) of ethylamine solution (70%) are added. A solution of 1.2 g (3.2 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacryloyl chloride in 40 ml of THF is added dropwise and the mixture is stirred at room temperature for one hour. The reaction medium is acidified with hydrochloric acid and extracted with ethyl ether, and the organic phase is separated out after settling has taken place, dried over magnesium sulphate and evaporated. The residue obtained is purified by chromatography on a column of silica eluted with dichloromethane. After evaporation of the solvents, 817 mg (68%) of N-ethyl-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-phenylacrylamide are collected, with a melting point of 158-9°C.

09619584-071900

EXAMPLE 28

N-(4-Hydroxyphenyl)-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)-phenylacrylamide.

5 In a similar manner to Example 27(a), by reaction of 1.2 g (3.2 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacryloyl chloride with 349 mg (3.2 mmol) of 4-hydroxyaniline, 810 mg of (57%) of N-(4-hydroxyphenyl)-3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl-
10 acrylamide are obtained, with a melting point of 240-1°C.

EXAMPLE 29

3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid morpholide.

15 In a similar manner to Example 27(a), by reaction of 1.3 g (3.4 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacryloyl chloride with 620 μ l of (7.12 mmol) of morpholine, 1.25 g (88%) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylic acid morpholide are
20 obtained, with a melting point of 158-9°C.

006720-18567960

EXAMPLE 30

Ethyl 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate.

In a similar manner to Example 1(d), by
5 reaction of 5 g (16.3 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)benzaldehyde with 4.79 g (21.2 mmol) of triethyl phosphonoacetate, 5 g (81%) of ethyl 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenylacrylate are obtained, with
10 a melting point of 70-2°C.

EXAMPLE 31

3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoic acid.

(a) 3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)acetophenone.
15

In a similar manner to Example 9(b), by
reaction of 5 g (20.3 mmol) of 3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthylboronic acid with 2.7 g (13.5 mmol) of 3-bromoacetophenone, 4.3 g (90%) of the
20 expected product are obtained, with a melting point of 89-90°C.

(b) Ethyl 3-[3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoate.

In a similar manner to Example 1(d), by
25 reaction of 3.7 g (11.5 mmol) of 3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)acetophenone with 3.9 g (17.3 mmol) of triethyl phosphonoacetate, 2.67 g (60%) of the expected ethyl ester are obtained

00619584-071900

in the form of a yellow oil.

(c) 3-[3-(3,5,5,8,8-Pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoic acid.

In a similar manner to Example 1(e), starting with 2.5 g (6.4 mmol) of the above ethyl ester, 1.63 g (70%) of 3-[3-(3,5,5,8,8-pentamethyl-5,6,7,8-tetrahydro-2-naphthyl)phenyl]but-2-enoic acid are obtained, with a melting point of 166-7°C.

EXAMPLE 32

Various solid formulations based on compounds according to the invention are illustrated in this example.

A- ORAL ROUTE

(a) 0.2 g tablet

15	- Compound of Example 1	0.001 g
	- Starch	0.114 g
	- Dicalcium phosphate	0.020 g
	- Silica	0.020 g
	- Lactose	0.030 g
20	- Talc	0.010 g
	- Magnesium stearate	0.005 g

(b) Drinkable suspension in 5 ml ampoules

	- Compound of Example 3	0.001 g
	- Glycerol	0.500 g
25	- 70% Sorbitol	0.500 g
	- Sodium saccharinate	0.010 g
	- Methyl para-hydroxybenzoate	0.040 g
	- Flavouring	qs

00619584-07900

- Purified water qs 5 ml

(c) 0.8 g tablet

- Compound of Example 5 0.500 g

- Pregelatinized starch 0.100 g

5 - Microcrystalline cellulose 0.115 g

- Lactose 0.075 g

- Magnesium stearate 0.010 g

(d) Drinkable suspension in 10 ml ampoules

- Compound of Example 2 0.050 g

10 - Glycerol 1.000 g

- 70% Sorbitol 1.000 g

- Sodium saccharinate 0.010 g

- Methyl para-hydroxybenzoate 0.080 g

- Flavouring qs

15 - Purified water qs 10 ml

B- TOPICAL ROUTE

(a) Ointment

- Compound of Example 21 0.020 g

- Isopropyl myristate 81.700 g

20 - Liquid petroleum jelly 9.100 g

- Silica ("Aerosil 200" sold by
Degussa) 9.180 g

(b) Ointment

- Compound of Example 9 0.300 g

25 - White petroleum jelly codex qs 100 g

00619584-071900

(c) Nonionic water-in-oil cream

	- Compound of Example 7	0.100 g
	- Mixture of emulsifying lanolin alcohols, waxes and oils ("Anhydrous Eucerin" sold by BDF)	39.900 g
5	- Methyl para-hydroxybenzoate	0.075 g
	- Propyl para-hydroxybenzoate	0.075 g
	- Sterile demineralized water qs	100 g

(d) Lotion

10	- Compound of Example 30	0.100 g
	- Polyethylene glycol (PEG 400)	69.900 g
	- 95% Ethanol	30.000 g

(e) Hydrophobic ointment

	- Compound of Example 25	0.300 g
15	- Isopropyl myristate	36.400 g
	- Silicone oil ("Rhodorsil 47 V 300" sold by Rhône-Poulenc)	36.400 g
	- Beeswax	13.600 g
	- Silicone ("Abil 300,000 cst" sold by Goldschmidt) qs	100 g
20		

(f) Nonionic oil-in-water cream

	- Compound of Example 14	0.500 g
	- Cetyl alcohol	4.000 g
	- Glyceryl monostearate	2.500 g
25	- PEG 50 stearate	2.500 g
	- Karite butter	9.200 g
	- Propylene glycol	2.000 g
	- Methyl para-hydroxybenzoate	0.075 g

005720-42561960

- Propyl para-hydroxybenzoate 0.075 g
- Sterile demineralized water qs 100 g

09619584-071900